

Words of wisdom. Bladder cancers arise from distinct urothelial sub-populations

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DOI:

[10.1016/j.eururo.2014.11.058](https://doi.org/10.1016/j.eururo.2014.11.058)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Bryan, RT & Ward, DG 2015, 'Words of wisdom. Bladder cancers arise from distinct urothelial sub-populations', *European urology*, vol. 67, no. 3, pp. 590-1. <https://doi.org/10.1016/j.eururo.2014.11.058>

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Bladder cancers arise from distinct urothelial sub-populations

Jason Van Batavia, Tammer Yamany, Andrei Molotkov, Hanbin Dan, Mahesh Mansukhani, Ekaterina Batourina, Kerry Schneider, Daniel Oyon, Mark Dunlop, Xue-Ru Wu, Carlos Cordon-Cardo and Cathy Mendelsohn.

Nature Cell Biology 2014; **16**: 982–991.

1 Expert's Summary

2 Using lineage-tracing techniques to indelibly label urothelial sub-populations in BBN carcinogenesis
3 mouse models, the authors found that papillary-like and CIS-like lesions developed from different
4 urothelial cell populations: non-invasive papillary lesions from intermediate cells of the urothelium
5 and CIS lesions from keratin-5 expressing basal cells. These findings support a model in which the
6 heterogeneity observed in bladder cancers is determined both by genetic changes and the cell
7 lineage from which the tumour originates. These findings also provide a plausible explanation for
8 clinical observations in humans regarding differences in natural history and prognosis of patients
9 with different types of non-muscle-invasive lesion, and suggest that the difference in clinical
10 outcomes may stem, at least in part, from a fundamental difference in the cell of origin.

11

12 Experts' Commentary

13 "Bladder cancer or bladder cancers?" is a question that urological scientists have been asking for
14 many years [1]: what are the molecular-genetic pathways that give rise to low-grade NMIBC, high-
15 grade NMIBC, CIS and MIBC? Some genetic abnormalities are common to all urothelial bladder
16 cancer (UBC) subgroups such as *TERT* promoter mutations, and others are associated with LG-NMIBC
17 (*FGFR3* mutations) or HG-NMIBC/CIS/MIBC (*TP53* mutations). Previous studies have suggested that
18 invasive or aggressive UBCs can develop from basal cells [2;3], and that some UBCs exhibit protein

19 and gene expression profiles indicative of an intermediate cell or luminal origin [4;5]. Van Batavia et
20 al have now directly demonstrated that papillary and CIS/invasive lesions arise from distinct
21 urothelial sub-populations, albeit in a model system which may not fully recapitulate tumourigenesis
22 in the human bladder. It now seems increasingly likely that the context provided by the 'cell of
23 origin' is key to both the oncogenic effects of the different genetic aberrations observed in LG-
24 NMIBC and HG-NMIBC/CIS/MIBC and to the very different behaviours of these two types of UBC.

25 Many questions still remain. How do papillary tumours progress to MIBCs? Do papillary tumours
26 always originate in the intermediate cell layer in humans? Why do patients seemingly successfully
27 treated for organ-confined disease relapse and succumb? Where do G3T1 tumours with mixed
28 mutation profiles originate? It is these fundamental questions that approaches based upon baseline
29 tumour characteristics, rather than outcomes, are yet to answer. The authors do not discuss
30 important processes such as epithelial-mesenchymal transition or the development of cancer stem
31 cells, but their elegant utilisation of morphologic approaches is refreshing in the era of next
32 generation sequencing and has contributed significantly to our understanding of this challenging
33 disease.

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Acknowledgements

RT Bryan's research has been funded by the Medical Research Council (UK), Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham. DG Ward's research has been funded by Birmingham Science City, Cancer Research UK, University Hospitals Birmingham Charities, and the University of Birmingham.

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